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NUTRITION REVIEWS

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FATNESS, FAT AND CORONARY HEART DISEASE

Until the twentieth century a generous measure of adiposity was valued as a mark of affluence, beauty, and health. Currently the only premium attaching to obesity in the western world is in life insurance contracts, reflecting a penalty rather than a tribute. Beginning with the report of Rogers (*Proc. Assn. Life Ins. Med. Dir. Amer., 280 (1901)*), which unexpectedly revealed a heightened mortality among insured overweights, a succession of medico-actuarial studies representing experience of individual insurance organizations and pooled intercompany data has uniformly shown that overweight is associated with a shortened life expectancy and an increased mortality from several diseases, notably cardiovascular disorders and particularly in men. These investigations have recently been summarized by Marks (*Human Biology* **28,** *217 (1956)*).*

On the basis of such actuarial data the conclusion has been drawn that, "Overweight shortens life, is an etiological factor in several principal diseases and hastens their downward course. Particularly important is the relationship between the accumulation of excess weight and the development of cardiovascular disease." (D. B. Armstrong, *et al., J. Am. Med. Assn.* **147,** *1007 (1951)*). This conclusion is being increasingly challenged, as in the report of the World Health Organization Study Group on Atherosclerosis and Ischemic Heart Disease (WHO Technical Report, No. 117, (1957)); *i.e.*, "There is no convincing evidence that relative obesity, (proportion of the body mass made up of fat) of itself, is a major factor in atherogenesis or the production of ischemic heart disease in man. Indirect indications from a consideration of the cholesterol-lipoprotein system in the blood serum are likewise inconclusive." Brozek and Keys (*Geriatrics* **12,** *79 (1957)*) have recently surveyed the relationship of overweight, obesity, and coronary heart disease, and question the validity of conclusions drawn from insurance statistics. On the basis of various clinical and necropsy studies they state that, "There is a surprising lack of evidence which would support the hypothesis that overweight is significantly involved in the development of atherosclerosis", and, "it appears that the frequency of obesity among individuals who develop coronary heart disease is not much greater than in the rest of the population." This reiterates the earlier statement of Keys (*Diabetes* **4,** *447 (1955)*) that, "The bulk of the evidence is opposed to the common belief that overweight is an important factor in the development of coronary heart disease or the production of myocardial infarction."

If unwarranted conclusions have at times been drawn intimating a direct causative role of obesity in arteriosclerotic heart disease, it appears equally extreme to dismiss any relationship on the basis of data where the "average" population serves as a control group. As in the instances of blood pressure and serum cholesterol (R. M. Daley, H. E. Ungerleider, and R. S. Gubner, *J. Am. Med. Assn.* **121,** *383 (1943)*; Gubner and Ungerleider, *Am. J. Med.* **6,** *60 (1949)*), where the average far exceeds optimal levels, so too is this the situation with weight.†

* An extensive intercompany build and blood pressure study is currently in progress.

† The "average" adult American population is in fact moderately obese, fat comprising some 20 per cent above lean, fat free, body weight of the average middle aged male, and 27 per cent among females. "Average" weight tables for adults of different ages do not reflect weight distribution in the population, for there is a marked skewing of mean from modal weight with advancing age due to the increasing prevalence of obesity. Thus in males of average height, the mean is sensibly the same as modal up to age 20, exceeds it by 5 pounds

TABLE 1

Mortality Ratios (Actual/Expected) among Moderate Underweights and Moderate Overweights

Study	Years Policies Issued	Follow-up	Age at Issue	Mortality Ratio (Actual/Expected)	
				Underweights	Overweights
Medico-Actuarial Mortality Investigation	1885–1908	to 1909		(minus 15 to 20 lbs.)	(plus 15 to 20 lbs.)
			50–56	92%	121%
			57–62	82%	125%
Medical Impairment Study	1885–1927	1909–1928		(minus 10% or more)	(plus 10 to 29%)
			40–49	80%	119%
			50–59	80%	115%
Provident Mutual Study	1920–1945	1937–1947	15–34	(minus 8 to 22 lbs.)	(plus 8 to 22 lbs.)
				87%	124%
				(minus 23 to 42 lbs.)	(plus 23 to 42 lbs.)
				90%	152%
				(minus 43 lbs. or more)	(plus 43 lbs. or more)
				74%	152%
Equitable Life Assurance Soc. of U. S.	1930–1939	to 1950	30–39	(minus 20 to 24%)	(plus 20 to 24%)
				71%	151%
				(minus 25 to 44%)	(plus 25 to 44%)
				72%	134% (+25 to 29%)
					212% (+30 to 34%)
					189% (+35 to 44%)
Equitable Life Assurance Soc. of U. S.	1940–1948	to 1949		(minus 10 to 29.9%)	(plus 10 to 29.9%)
			30–49	86%	107%
			50 and over	90%	117%
Metropolitan Life (Women)	1922–1936	to 1936		(minus 15 to 24%)	(plus 15 to 24%)
			under 30	100%	100%
			50 and over	83%	116%

If the relationship of fatness to longevity and cardiovascular disease is to be properly assessed the most appropriate control group would appear to be not the average population, but a group with minimal fat content, *i.e.*, those significantly underweight with respect to the average population.

Table 1 presents a comparison of the mortality ratios of comparable underweight and overweight groups in several insurance studies of mortality experience according to build. In the table moderate underweights are compared with moderate overweights in terms of pounds or percentage variation from average, according to data employed in these investigations. In all these studies, as well as others, the mortality ratios rose steadily with increasing degrees of overweight beyond the moderately overweight groups presented, but figures for grossly obese persons are not included since the table is confined to a comparison of equivalent degrees of overweight and underweight. In earlier studies such as the MAMI study of 1909, the favorable mortality experience of underweights was

between 20 and 40, by 10 pounds between 40 and 50, and by 12 pounds above 50.

Although weight tables, at best, whether average, modal or ideal do not provide a regularly accurate index of adiposity, there are limitations to more direct measurements of fatness, even with such a simplified method as skinfold thickness calipers, since this is not generally available. A simple gauge of body fatness is provided by the index height (in inches) minus abdominal girth (male height with, female height without, shoes). Average adult range is 40 to 30, representing 10 per cent fatness at a numerical index of 40, to 30 per cent fatness at an index of 30. The mean index is the familiar "perfect 36," but this represents 18 per cent fatness, and the ideal is 40, or 10 per cent fatness.

evident only in older persons because of the high tuberculosis mortality among young underweights at that time, but in more recent studies the favorable mortality of underweights as compared to overweights has been even more striking in younger than older males. Although underweights fare better than overweights at all periods, the disparity increases with time. Thus, while an appreciable mortality rate difference was found in the short term Equitable study, which embraced a one to nine-year follow-up, (Table 1) a far more striking difference was observed in the long term study which covered a six- to 20-year period. In the latter study the mortality rate of the overweights was more than twice that of the comparably underweight groups.

Although cardiovascular disease accounts for more than half the mortality of insured lives, and the greatest percentage represents coronary heart disease, gross mortality data offer only an indirect indication of an association between overweight and coronary disease. Since the clinical recognition of coronary artery disorders and myocardial infarction is relatively recent, earlier insurance studies such as the MAMI and MIS did not provide specific information on this subject. However, it was observed in the Medical Impairment Study that deaths from organic diseases of the heart were 50 per cent greater in those 50 pounds or more overweight than in those 25 pounds or more underweight.

In the Equitable Life study of policy issues of 1940 to 1948, observed through their 1949 anniversaries, analysis was made of male deaths due to circulatory disease. The results are presented in Table 2. The findings are striking, with a threefold increase in cardiovascular disease mortality as the body build progressed from 10 to 29 per cent underweight to 30 to 39.9 per cent overweight. Slightly over three fourths of all deaths from circulatory diseases were due to angina pectoris and coronary disease. Specifically the ratios of coronary to total circulatory disease deaths was 67 per cent in the 10 to 29 per cent underweights, and 76, 77 and 78 per cent respectively in the "average," +10 to 29.9 per cent, and +30 to 39.9 per cent overweight classes. This further suggests that underweight is associated with less coronary disease than is the case in "average" or overweight groups. The Metropolitan Life Study on women likewise analyzed mortality rates from angina pectoris and coronary artery disease. Among those 5 to 24 per cent underweight the actual deaths from these causes were 75 per cent of those expected. Among females 15 to 34 per cent overweight the mortality ratio was 143 per cent. A further indication that the excess mortality rate in overweight as compared to underweight women is due to coronary disease is suggested in the Metropolitan Life data presented in Table 1. Among younger women, who are relatively immune from coronary disease, there is no difference in mortality between underweights and overweights; in women beyond the menopause (policy issue at age 50 and over) the difference between underweight and overweight is similar to that in males. In general the adverse association between obesity and mortality is far more striking in males than in females.

TABLE 2

Male Deaths Due to Circulatory Diseases

(Actual/Expected)

Build	Issue Age 30–49	50 & over	All ages
−10 to −29%	69% (A/E)	81%	73%
−9.9 to +9.9%	114	104	110%
+10 to +29.9%	132	136	136%
+30 to +39.9%	260		225%

Pathological as well as actuarial studies have shown significant differences in coronary disease in overweights as compared to underweights. Thus, in the study of Ackerman, Dry and Edwards at the Mayo Clinic (*Circulation* **1**, *1345 (1950)*), it was found that the degree of coronary sclerosis was greater in overweight than underweight

women at all ages from 30 to 89. It is of interest that the degree of coronary sclerosis was identical among obese women and women of average weight.

Similar observations based on necropsy examination were reported by Wilens (*Arch. Int. Med.* **79,** *129 (1947)*). He found advanced degrees of coronary atherosclerosis to be almost as common in women of average build (20.0 per cent) as in the obese (22.6 per cent), whereas in poorly nourished women advanced degrees of coronary atherosclerosis occurred far less commonly (12.1 per cent). In males the difference between obese and underweights was more striking. Advanced degrees of coronary atherosclerosis were present in 40.8 per cent of obese, 18.7 per cent of average build, and 12.5 per cent of underweight males.

Nutritional classification based on build at necropsy is admittedly not representative of lifetime weight because of weight loss in terminal illnesses. Wilens attempted to estimate this factor by comparing the nutritional status of the patients necropsied, with visitors to Bellevue Hospital, who were presumably of the same background. Ten per cent of the necropsied males were obese, compared to a 25 per cent incidence of obesity among male hospital visitors; 50 per cent of those necropsied were underweight, compared to 10 per cent among hospital visitors. Wilens stressed that terminal weight losses tended to minimize the differences observed, and concluded, "that the relationship between obesity and atherosclerosis is a much more striking one than the findings here indicate and that the state of nutrition is of great importance in the genesis of this disease."

Pathological studies require retrospective assumptions of body build throughout adult life, and actuarial studies involve prospective assumptions of build from the time of policy issue to the time of death. To some degree this limits conclusions which may be drawn from such data. However, this qualification does not apply to the recent joint epidemiological reports from Framingham, Massachusetts, Albany, New York, and Los Angeles, in which the rate of development of coronary heart disease was studied over a two- to four-year period (*Am. J. Pub. Health* **47,** (*Supplement*) *April (1957)*).

In the Framingham study, in a four-year period of observation of males 45 to 62, the new coronary disease rate of those 20 per cent or more above median weight (123 per 1,000) was three times that of those less than median weight (40 per 1,000). The Albany study comprised a 31-month study period of male civil service employees, of age 39 to 55. Underweights were not separately classified. The new disease rate in those less than 20 per cent over ideal was 19 per 1,000, in those 20 to 39 per cent over ideal, 24 per 1,000, and in those 40 per cent or more over ideal, 65 per 1,000. Increase of body weight of more than 20 per cent above any weight level existing at the age of 25 was associated with a doubled risk of developing ischemic heart disease. The Los Angeles study likewise comprised civil service employees observed over two to three years. Among males 40 to 54 years of age, the incidence of coronary disease was five times greater in those of heavy weight than in those of light weight. In the entire group, age 40 to 70, the coronary disease incidence was three times greater in those classified heavy, as in those classified as light.

These epidemiological studies are of relatively short duration, and more significant conclusions will emerge with a longer period of follow-up. Since the adverse relationship of obesity to mortality increases with increasing length of time, as revealed by comparison of the Equitable short term and long term studies in Table 1, it may be anticipated that greater differences in coronary disease incidence will be reflected in subsequent studies of these groups.

Although coronary disease and atherosclerosis are usually considered interchangeably, it is increasingly evident that there are distinct processes and associations involved in clinical coronary heart disease, beyond the basic atherosclerotic lesion. Thus, while a

relationship exists between fatness and coronary heart disease, no such association obtains for arteriosclerosis in other sites, as in the aorta (Gubner, *Trans. Assn. Life Ins. Med. Dir. Amer.* **34,** *20 (1950)*). The degree of atherosclerotic lesions in the aorta was found to be identical in underweights and overweights in the extensive study of Holman *et al.* (*Ibid.* **40,** *86 (1956)*), and also in the study of Cinti and de Biase, who observed no differences between obese and non-obese persons in other arteries as well (*Arch. "de Vecchi" anat. pat.* **19,** *857 (1953)*). Similarly, despite the vastly greater frequency of coronary heart disease in males compared to females, in whites compared to negroes, and in Americans compared to other nationalities (Spain, Puerto Rico, Costa Rica, Guatemala and South Africa), Holman was able to demonstrate almost no difference in the degree of aortic atherosclerosis among these various groups. Faber and Lund (*Arch. Path.* **48,** *351 (1949)*) likewise were unable to demonstrate any differences in the degree of aortic arteriosclerosis between those of normal weight and moderately or markedly obese persons, or between men and women. The atherosclerotic lesion, as Duff and McMillan (*Am. J. Med.* **11,** *92 (1951)*) and Holman have shown, regularly begins early in life, with approximately a twenty-year lag between the initial fatty streak atheroma and fibrous pearly plaque formation. The progression of the lesions is primarily a function of age, with the degree of involvement accentuated by hypertension and diabetes (Holman, Faber and Lund, Ackerman, Dry and Edwards). There is no correlation between the lipid content of the aorta and the serum cholesterol (K. E. Lande, and W. M. Sperry, *Arch. Path.* **22,** *301 (1936)*), except perhaps in hypercholesterolemic xanthomatosis in which atheromata are increased, and extreme hypocholesterolemia, in which there is a decrease. In the coronary arteries, unlike the aorta, atherosclerosis is greater in men than in women (Ackerman, Dry and Edwards), but the difference is small compared to the enormous disparity in clinical coronary disease between the sexes.

Evidently there are at least two basic processes in coronary disease, with probable distinct pathogenetic backgrounds. The first is atherosclerosis, which, when of advanced stenotic degree, carries an overall correlation with clinical coronary heart disease (Ackerman, Dry and Edwards). The second constitutes the complicating thrombotic lesion which precipitates the more acute and recognizable forms of coronary disease such as myocardial infarction.

Such association as obtains between body fatness and coronary heart disease lies in relation to the later complications of coronary atherosclerosis such as thrombosis and not the early lesions of atherosclerosis which form the "anlage" of clinical coronary disease. Whether build, sex and ethnic differences in coronary heart disease incidence have their common denominator in certain facets of lipid metabolism has not been positively established. There are well documented sex, age and build differences in serum lipid and lipoprotein patterns (E. M. Russ, H. A. Eder, and D. P. Barr, *Am. J. Med.* **11,** *468 (1951)*; L. A. Lewis and I. M. Page, *Circulation* **7,** *707 (1953)*; J. W. Gofman *et al.*, *J. Am. Dietet. Assn.* **30,** *317 (1954)*; A. Keys *et al.*, *Clin. Chem.* **1,** *34 (1955)*). Particularly publicized have been ethnic differences in calorie, total and type of fat consumption, as well as other dietary constituents, which seemingly correlate with coronary heart disease prevalence. However, as Yerushalmy and Hilleboe incisively indicate, no specific association between fat intake and coronary disease is established by such ethnic data (*N. Y. State J. Med.* **57,** *2343 (1957)*).* In the case of obesity closer relationship to lipid metabolism may be inferred, for body fat is the visible stratum of lipid metabolism. The nature of the association between fatness and coronary disease, therefore, can be viewed properly only in context to the overall pattern of lipid metabolism in obesity.

* Also, Yudkin, J., *Lancet* **273,** *155, (1957)*.

Albeit not of major degree there are differences in the obese, as compared with others, with respect to a) fat consumption, b) storage and transport, and c) utilization.

a) The dietary excess of obese persons with respect to calories may not be great, but a survey of food habits by Morgan (*Food and Nutrition News* **28,** *#5 (1957)*) revealed an increase in fat consumption among the obese.

b) Fat depots are not inert, but metabolically very active, synthesizing fat from serum fatty acids and carbohydrates. Fat storage requires the agency of insulin, and when the amount of adipose tissue is large there is stress on the insulin mechanism, reflected by predisposition to diabetes, both latent and overt. Few, if any factors are so positively related to coronary artery disease as diabetes mellitus. The disturbance in lipid metabolism in obesity is similar to that in diabetes, *i.e.*, a trend toward high fasting serum fatty acid levels and an augmented and protracted post-prandial rise (E. F. Hirsch and L. Carbonaro, *Arch. Int. Med.* **86,** *519 (1950)*; J. Pomeranze *et al.*, *Circulation* **10,** *742 (1954)*). These abnormalities are more evident in extreme obesity and when diabetes is severe. In diabetic ketosis insulin lack results in mobilization of fat from adipose tissue with extreme rises in serum triglyceride, and accompanying secondary elevation of other serum lipids such as cholesterol, whose synthesis is augmented from the increased pool of active acetate fragments of fatty acid oxidation. At the other extreme may be cited increased lipogenesis where an adequacy of insulin accompanies hyperglycemia, illustrated by the frequent large size fetus of diabetic mothers.

c) Lessened utilization of fat in the obese is related most simply to a lessened degree of physical activity and basal calorie requirement with advancing age, which is recognized to play at least as important a role in the genesis of obesity as excess calorie consumption (H. Pollack, *Modern Concepts of Cardiovasc. Dis.* **26,** *371 (1957)*). Vigorous physical activity, disposing of excess calories by energy expenditure, prevents weight gain and hyperlipemia otherwise induced by high fat (150 to 175 g.) high caloric (6,000 calories) diets (G. V. Mann *et al.*, *New Engl. J. Med.* **253,** *349 (1955)*).

Heightened calorie and fat consumption, storage impairment, and decreased fat utilization (now known to be the major direct metabolic fuel) have the common net effect of loading the serum transport mechanisms. This is reflected relatively crudely by serum cholesterol levels, which has been the serum lipid fraction to have received widest study, and which is usually invoked as the causative agent in arteriosclerosis and coronary disease.

One may seriously question that cholesterol represents a primary metabolic factor in the clinically important thrombotic aspect of coronary disease. Some years ago the view was expressed by the author that, "If cholesterol is the actual culprit in arteriosclerosis, fat is an active accomplice" (*Am. J. Med.* **6,** *60 (1949)*). On the basis of more recent developments, such as those relating chylomicra (D. S. Robinson and J. C. F. Poole, *Quart. J. Exp. Physiol.* **41,** *36 (1956)*), fatty acids (Poole, *Brit. J. Exp. Path.* **36,** *248 (1955)*), and certain phospholipids, such as phosphatidylethanolamine (J. R. O'Brien, *Lancet* **272,** *1213 (1957)*) to thrombosis and inhibition of fibrinolysis, one may revise this concept at least in respect to coronary thrombosis. Fat or phospholipid may be arraigned as the culprit in thrombosis, with cholesterol possibly functioning to exert a protective role via its opposing effect on surface activity, as a deterrent to such processes as thrombosis and hemolysis. There is evidence that cholesterol does indeed have an antithrombogenic as well as antihemolytic effect, opposing the action of phospholipid (J. B. Proost, *Acta Med. Scandinav.* **116,** *396 (1944)*).

Cholesterol is not an inert serum constituent, but is intimately associated with low density lipoproteins in fat transport, pack-

aging triglycerides from their initial large chylomicron form to smaller lipomicron units, or lipoprotein complexes, which are acted on by the lipoprotein lipase clearing mechanism to release fatty acids. In these vehicular forms, as lipomicrons, non-esterified fatty acids, or fatty acid-albumin complex, fat is taken up by tissues, such as the myocardium, and metabolized in energy reactions.

When fat is ingested and serum triglycerides rise there is an accompanying substantial elevation of serum phospholipids, probably deriving from the ingested fat (R. J. Havel, *J. Clin. Invest.* **36,** *848 (1957)*). It is of interest that the elevation of serum phospholipids, which outlasts the triglyceride increase, parallels changes in blood coagulation (aggregation and adhesiveness) which appear after the peak of lipemia has been passed, and develop to their maximum as the lipemia clears (D. F. Cullen and R. L. Swank, *Circulation* **9,** *335 (1954)*). Changes in cholesterol, which may be homeostatic, also occur following fat ingestion, namely a reversible transfer of cholesterol from lipoproteins of low to lower density, and a synthesis of cholesterol in the liver from the active acetate fragments of neutral fat. An elevation of serum cholesterol occurs not only following fat administration, but also when phosphatides are ingested or when an elevation is induced by surface active agents (M. Friedman and S. Byers, *Am. J. Physiol.* **186,** *13 (1956)*).

Cholesterol is not, however, merely a passive mirror of serum fat and phospholipids, but may itself play a regulatory role influencing other serum lipids. It is a potent inhibitor of serum lipase, and a close inverse correlation exists between serum lipase activity and the level of serum cholesterol (I. Remesow and N. Tavaststyerna, *Ztschr. f. d. ges. Exper. Med.* **87,** *613 (1933)*). Since lipoprotein lipase is involved in the clearing of triglycerides, cholesterol levels may influence this activity. It is of interest that protracted alimentary lipemia, reflecting delayed clearing, occurs in coronary heart disease (D. W. Barritt, *Brit. Med. J., Sept. 15, 1956, p. 640*), as well as in diabetes and obesity (Hirsch and Carbonaro, Pomeranze *et al.*) in all of which serum cholesterol levels tend to be high. To some degree, then, elevation of serum cholesterol may be a cause as well as a result of increased serum triglycerides.

Both rise and fall of cholesterol, as well as phospholipid, lag behind triglyceride changes following fat ingestion. Although there are multiple interrelationships among the serum lipids, in general phospholipids and cholesterol may be viewed as the wake and wash of triglyceride tides. In consequence, the temporal changes in cholesterol, phospholipids and lipoproteins do not parallel serum triglycerides, but a cumulative increase may occur in the serum level, notably of the β-lipoprotein cholesterol, which is only slowly adjusted by biliary and intestinal disposal.

Increase in serum fatty acids, cholesterol and low density lipoproteins occur not only when fat is ingested, but also when an excess of calories in the form of carbohydrates and proteins is supplied (W. J. Walker *et al.*, *Am. J. Med.* **14,** *654 (1953)*). Indeed it is the view of Mann, a co-author in this study, that total calorie intake is the critical factor and he voices skepticism that dietary fat is either the sole, or even an important, factor in the regulation of the serum lipid levels (*Am. J. Clin. Nutrition* **3,** *230 (1955)*; **4,** *76 (1956)*). There is ample evidence that dietary constituents other than fat profoundly influence lipid metabolism. Lossow and Chaikoff (*Arch. Biochem. Biophys.* **57,** *23 (1955)*) have shown that carbohydrate depresses fatty acid breakdown. Lipid synthesis also occurs from carbohydrate. Individual variations in fatty acid and cholesterol synthesis from glucose oxidation in the liver depend on the particular glycolytic pathway taken, with greatest stimulation of fatty acid and cholesterol synthesis deriving from the hexosemonophosphate pathway (M. D. Sip-

erstein and V. M. Fagan, *J. Clin. Invest.* **36,** *929 (1957)*).

Viewed in this light it is understandable why cholesterol becomes increased when serum fats are recurrently elevated, whether by:

a) increased consumption of fat or calories.

b) mobilization from storage fat (insulin lack, stress (or smoking) with accompanying adrenal stimulation and epinephrine release).

c) decreased peripheral utilization, *e.g.* decreased physical activity or hypometabolism.

d) impaired serum transport mechanisms involving conversion of fat into the metabolically usable forms of albumin-fatty acid and non-esterified fatty acid, *e.g.*, hypoalbuminemia as in nephrosis, clearing factor abnormalities.

e) less readily metabolized compared to more readily metabolized fats, *i.e.*, saturated vs. unsaturated fats.

f) hepatic pathways favoring lipid synthesis rather than oxidation.

With the resulting elevation of serum lipids, by whichever factor, when complications such as thrombosis ensue, cholesterol in its lipoprotein complex becomes enmeshed in the fibrin thrombus, and because of its insolubility is a conspicuous and enduring vestige. Cholesterol cannot readily be exculpated with the explanation that it is innocently enmeshed in fibrin thrombi, or that it may even play a beneficent role in opposing the thrombogenic action of other lipids. This is counter to a long line of experimental studies on atherogenesis, including observations that a high phospholipid to cholesterol ratio inhibits experimental atherosclerosis by solubilizing cholesterol (Duff and McMillan). However, a different situation may obtain entirely with respect to lipid factors in thrombosis, which is the determinant of clinical coronary disease, than is the case in atheromatous lipid deposition. A high phospholipid to cholesterol ratio may favorably influence atherogenesis but it increases blood coagulability (Proost). It appears probable that there are multiple metabolic factors determining the different pathological processes of atheroma formation and thrombosis, both of which are involved in the evolution of coronary heart disease. What is advantageous in serum lipids with respect to atheromatous deposition may not apply to thrombosis.

There are no firm lessons which can presently be drawn with respect to control of the lipid factors in coronary disease. There is, however, a burden of proof upon those who would lower serum cholesterol, *per se*, irrespective of the means employed, to show that benefit results. It seems clear that, at least concerning the thrombotic factor in coronary disease, cholesterol is not the noxious agent, and fats and phospholipids merit more attention. In general, cholesterol follows in the wake of and reflects metabolism of triglycerides and phospholipids. From what is presently known, it would appear most rewarding and practical to maintain low levels of serum fat by the simple virtues; *i.e.*, 1) abstemiousness in diet, with low intake of calories, fat and especially animal fat (total and particularly at one meal), 2) adequate physical activity, and 3) minimal psychological stress, and, perhaps, reduced smoking. If the visible result of these measures, which reduce lipemia, is that of a lean and vigorous population, it may be anticipated that there will be less coronary disease than now exists in our presently relatively obese and physically inactive American populace.

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erstein and V. M. Fagan, *J. Clin. Invest.* **36,** *929 (1957)*).

Viewed in this light it is understandable why cholesterol becomes increased when serum fats are recurrently elevated, whether by:

a) increased consumption of fat or calories.

b) mobilization from storage fat (insulin lack, stress (or smoking) with accompanying adrenal stimulation and epinephrine release).

c) decreased peripheral utilization, *e.g.* decreased physical activity or hypometabolism.

d) impaired serum transport mechanisms involving conversion of fat into the metabolically usable forms of albumin-fatty acid and non-esterified fatty acid, *e.g.*, hypoalbuminemia as in nephrosis, clearing factor abnormalities.

e) less readily metabolized compared to more readily metabolized fats, *i.e.*, saturated vs. unsaturated fats.

f) hepatic pathways favoring lipid synthesis rather than oxidation.

With the resulting elevation of serum lipids, by whichever factor, when complications such as thrombosis ensue, cholesterol in its lipoprotein complex becomes enmeshed in the fibrin thrombus, and because of its insolubility is a conspicuous and enduring vestige. Cholesterol cannot readily be exculpated with the explanation that it is innocently enmeshed in fibrin thrombi, or that it may even play a beneficent role in opposing the thrombogenic action of other lipids. This is counter to a long line of experimental studies on atherogenesis, including observations that a high phospholipid to cholesterol ratio inhibits experimental atherosclerosis by solubilizing cholesterol (Duff and McMillan). However, a different situation may obtain entirely with respect to lipid factors in thrombosis, which is the determinant of clinical coronary disease, than is the case in atheromatous lipid deposition. A high phospholipid to cholesterol ratio may favorably influence atherogenesis but it increases blood coagulability (Proost). It appears probable that there are multiple metabolic factors determining the different pathological processes of atheroma formation and thrombosis, both of which are involved in the evolution of coronary heart disease. What is advantageous in serum lipids with respect to atheromatous deposition may not apply to thrombosis.

There are no firm lessons which can presently be drawn with respect to control of the lipid factors in coronary disease. There is, however, a burden of proof upon those who would lower serum cholesterol, *per se*, irrespective of the means employed, to show that benefit results. It seems clear that, at least concerning the thrombotic factor in coronary disease, cholesterol is not the noxious agent, and fats and phospholipids merit more attention. In general, cholesterol follows in the wake of and reflects metabolism of triglycerides and phospholipids. From what is presently known, it would appear most rewarding and practical to maintain low levels of serum fat by the simple virtues; *i.e.*, 1) abstemiousness in diet, with low intake of calories, fat and especially animal fat (total and particularly at one meal), 2) adequate physical activity, and 3) minimal psychological stress, and, perhaps, reduced smoking. If the visible result of these measures, which reduce lipemia, is that of a lean and vigorous population, it may be anticipated that there will be less coronary disease than now exists in our presently relatively obese and physically inactive American populace.

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